

**REMARKS****I. Introduction**

These amendments and remarks are being filed in response to the Final Office Action dated June 11, 2007. For the following reasons this amendment should be entered, the application allowed, and the case passed to issue. No new matter is introduced by this amendment.

If this application is not allowed, Applicants submit this amendment should be entered upon filing an appeal, as it reduces the issues for appeal.

Claims 1-21 are pending in this application. The Examiner withdrew claims 1-5 and 8-20 following a restriction requirement. Claims 7 and 21 have been cancelled. Claim 6 has been amended to incorporate the limitations of cancelled claims 7 and 21 and to clarify the inter-relationships of the components. Support for the amendments is found at page 14:16-19.

Claims 6, 7 and 21 were rejected 35 U.S.C. § 112 and claims 6 and 7 were rejected under 35 U.S.C. § 103(a).

**II. Rejection under 35 U.S.C. § 112, first paragraph**

The Examiner rejected claims 6, 7 and 21 under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter not described in the specification in such a way as to reasonably convey possession or enablement of the invention to one skilled in the art. Applicants respectfully disagree. The Examiner suggested amending the claims to indicate that the secondary anti-immunoglobulin antibody binds to the primary antibody. As supported in the originally filed Specification at page 14: 16-19, claim 6 as amended recites:

A kit for measuring of prostacyclin in plasma comprising:

(1) a 6-keto-  $\text{PGF}_{1\alpha}$  -aequorin conjugate; wherein said conjugate comprises a cysteine-free aequorin mutant;

wherein said cysteine free aequorin mutant comprises a unique cysteine residue introduced at amino acid positions 69, 70, 74 or 76, and

wherein the 6-keto-  $\text{PGF}_{1\alpha}$  binds to the sulfhydryl group of the cysteine

(2) an anti-6-keto-  $\text{PGF}_{1\alpha}$  primary antibody; and

(3) a secondary anti-6-keto-  $\text{PGF}_{1\alpha}$  immunoglobulin antibody that binds to the primary antibody.

Claim 6 clearly defines a conjugate, a primary antibody and a secondary antibody that binds to the primary antibody. Applicants respectfully submit that the amendment to claim 6, per Examiner's suggestion is adequately enabled and supported by the specification and thereby obviates the rejection of claims 6 and dependent claim 2 and 21.

### **III. Rejection under 35 U.S.C. § 112, second paragraph**

Claims 6, 7 and 21 were rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Applicants respectfully disagree.

The Examiner alleges that the interrelationships of the components is not clear and as to claim 21, that there is no antecedent basis for the cysteine free aequorin mutant and the sulfhydryl group and that it is not known how a conjugate is bound to a sulfhydryl group .

As discussed above in reference to the rejection under 35 U.S.C. § 112, first paragraph, claim 6 has been amended to clearly define the interrelationships of the components. Particularly, that the secondary antibody binds to the primary antibody.

Moreover, claim 6 defines the cysteine free aequorin mutant as comprising a unique cysteine residue introduced at amino acid 69, 70, 74 or 76, and wherein the 6-keto-  $\text{PGF}_{1\alpha}$  binds to the sulfhydryl group of the cysteine.

A person having ordinary skill in the art would recognize that cysteine has the form  $\text{C}_3\text{H}_7\text{NO}_2\text{S}$ , with a SH or sulfhydryl group. Moreover, wild-type aequorin originally has three cysteine residues. In the aequorin of the instant disclosure and claim, the cysteine residues of wild-type aequorin are removed in order to provide a more stable aequorin than the wild-type form. Next, a location is selected where one unique cysteine is introduced by site-directed mutagenesis for use as a site-selective location for attachment of the antigen, 6-keto-  $\text{PGF}_{1\alpha}$ .

In this manner the 6-keto-  $\text{PGF}_{1\alpha}$  binds to the sulfhydryl group of the cysteine that is introduced in the aequorin mutant.

Accordingly, Applicants respectfully request withdrawal of the rejection as amended claim 6 clearly defines the subject matter of the invention.

#### **IV. Rejection under 35 U.S.C. § 103(a)**

Claim 6 was rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pradelles et al. (Anal. Chem. 57: 1170, 1985) in view of Kosak US 4,606,364, Stults US 5,486,455 or Liotta et al. US 5,942,407.

Claim 7 was rejected under 35 U.S.C. § 103(a) allegedly being unpatentable over Pradelles in view of either Kosak, Stults or Liotta and further in view of Lewis et al., (Bioconjugate Chem. 11: 65, 2000). Applicants respectfully disagree with the Examiner's position. However, in the interest of expediting prosecution, claim 6 has been amended to incorporate the limitations of dependent claims 7 and 21.

As amended claim 6 requires that the cysteine free aequorin mutant comprises a unique cysteine residue introduced at amino acid 69, 70, 74 or 76. None of the references, either alone or in combination teach this limitation. Moreover, Lewis et al., merely discloses a mutant aequorin containing cysteine residues at positions 5, 53, 71 and 84, not at positions 69, 70, 74 or 76 as presently claimed.

In view of the above amendments and remarks, Applicants submit that this amendment should be entered, the application allowed, and the case passed to issue. If there are any questions regarding this Amendment or the application in general, a telephone call to the undersigned would be appreciated to expedite the prosecution of the application.

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To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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